Remarks

The Final Office Action mailed July 24, 2003, as been received and reviewed. Claim 38 having been amended, the pending claims are claims 27-39.

Claim 38 has been rewritten in independent form as kindly suggested by the Examiner.

Reconsideration and withdrawal of the rejections are respectfully requested.

Rejection under 35 U.S.C. §102(b)

The Examiner rejected claims 36, 37, and 39 under 35 U.S.C. §102(b) as being anticipated by Ruenitz et al. (J. Med. Chem., 1996), with Jones et al. (J. Med. Chem., 1992) added to support inherency in response to arguments. Specifically, the Examiner noted that Ruenitz et al. cites Jones et al. to provide experimental details that include compound **9** in DMSO, and alleged that the disclosure of compound **9** in DMSO by Ruenitz et al./Jones et al. is a disclosure of a pharmaceutical composition. Applicant respectfully traverses the rejection, and submits that the disclosure of compound **9** in DMSO by Ruenitz et al./Jones et al. is not a pharmaceutical composition as presently claimed for at least the reasons presented herein below.

Specifically, independent claim 36 recites "a pharmaceutically acceptable carrier." The Examiner alleged that the disclosure of compound **9** in DMSO by Ruenitz et al./Jones et al. is a pharmaceutical composition, apparently implying that DMSO is a pharmaceutically acceptable carrier. Applicant respectfully traverses the implication.

In describing dimethyl sulfoxide (DMSO), Remington's Pharmaceutical Sciences, Volume 18 (1990) (EXHIBIT A) stated the following:

> During the course of its agricultural use as a solvent it was discovered to relieve arthritic pain, and it soon became used rather widely and promiscuously in the topical treatment of various collagen diseases. The discovery of DMSO-induced lens opacities in animals resulted in termination of these uses.

Thus, although DMSO has been studied for topical delivery of drugs, the DMSO-induced lens opacities observed in animals terminated those uses. In view of the remarks presented herein above, Applicant respectfully submits that one of skill in the art would not consider DMSO to be a pharmaceutically acceptable carrier for topical delivery of the claimed compositions.

In view of the remarks presented herein, Applicant respectfully submits that Ruenitz et al./Jones et al. fail to disclose a pharmaceutical composition of compound **9**, and requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §102(b).

Allowed Claims

Applicant notes with appreciation that claims 27-35 have been allowed.

Objection to the Claims

The Examiner objected to claim 38 as being dependent upon a rejected base claim, but noted that claim 38 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claim. Claim 38 having been rewritten in independent form, Applicant respectfully requests that the objection to claim 38 be withdrawn, and that claim 38 be passed on to allowance.

Summary

It is respectfully submitted that all the pending claims are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicant's Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
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October 24, 2003
Date

By: _____
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CERTIFICATE UNDER 37 CFR §1.8:
The undersigned hereby certifies that the Transmittal Letter and the paper(s), as described hereinabove, are being transmitted by facsimile in accordance with 37 CFR §1.6(d) to the Patent and Trademark Office, addressed to Assistant Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 24 day of October, 2003, at 9:39 a.m. (Central Time).

By: _____
Name: Rachel Englund Graham

Exhibit A

Remington's Pharmaceutical Sciences

18

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The use of structural formulas from USAN and the USP Dictionary of Drug Names is by permission of The USP Convention. The Convention is not responsible for any inaccuracy contained herein..

NOTICE—This text is not intended to represent, nor shall it be interpreted to be, the equivalent of or a substitute for the official United States Pharmacopeia (USP) and/or the National Formulary (NF). In the event of any difference or discrepancy between the current official USP or NF standards of strength, quality, purity, packaging and labeling for drugs and representations of them herein, the context and effect of the official compendia shall prevail.

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[64490-92-2] $C_{15}H_{14}NNaO_3.2H_2O$ (315.31).

Preparation—The corresponding acetonitrile is obtained by a Friedel-Crafts reaction between 1-methylpyrrole-2-acetonitrile and *p*-methylbenzoyl chloride; after separation from the 4-aroyl isomer produced simultaneously, by fractional crystallization and/or adsorption chromatography, the acetonitrile is converted to tolmetin by saponification and subsequently to its sodium salt (*J Med Chem 14:* 646, 1971).

Description—Light yellow, crystalline powder; pK_a 3.5 (free acid).
Solubility—Freely soluble in water; slightly soluble in alcohol.

Uses—A nonsteroidal compound that has anti-inflammatory, analgesic and antipyretic activities. Its mode of action is unknown; inhibition of prostaglandin synthesis may be responsible for its anti-inflammatory action. In patients with rheumatoid arthritis various manifestations of its anti-inflammatory and analgesic actions are observed, but there is no evidence of alteration of the progressive course of the underlying disease.

The drug is absorbed rapidly and almost completely with peak plasma levels being reached within 30 to 60 min after an oral therapeutic dose (40 μg/mL after a 400-mg dose). It is bound approximately 99% to plasma proteins; the mean plasma half-life is about 1 hr. Essentially all of a dose is excreted in the urine within 24 hr, either as an inactive oxidative metabolite or as conjugates of tolmetin.

The drug is indicated for the relief of signs and symptoms of rheumatoid arthritis, both of acute flares and long-term management of the disease. Safety and effectiveness in patients who are incapacitated, largely or wholly bedridden or confined to a wheelchair, with little capacity for self-care (Functional Class IV rheumatoid arthritis) have not been established. The drug is comparable to aspirin and to indomethacin in controlling disease activity but the frequency of the milder gastrointestinal adverse effects is reported to be less than in aspirin-treated patients and the incidence of CNS adverse effects less than in indomethacin-treated patients. Concomitant administration of this drug and aspirin is not recommended since there does not appear to be any greater benefit from the combination over that achieved with aspirin alone and the potential for adverse reactions is increased.

It is contraindicated in patients demonstrated to be hypersensitive to the drug, and also in those in whom aspirin and other nonsteroidal anti-inflammatory drugs induce symptoms of asthma, rhinitis or urticaria. In patients with active rheumatoid arthritis who also have an active peptic ulcer, treatment with nonulcerogenic drugs should be attempted; if it must be given, the patient should be observed closely for signs of ulcer perforation or severe gastrointestinal bleeding. As it is eliminated primarily by the kidneys, patients with impaired renal function should be monitored closely and dosage reduced or discontinued if necessary. As it prolongs bleeding time, patients who may be affected adversely should be observed carefully when treated with the drug. Patients with compromised cardiac function should be treated with caution because the drug causes some retention of water and sodium, with a resultant mild peripheral edema.

The most frequent adverse reactions are gastrointestinal and include, in descending order of frequency, epigastric or abdominal pain or discomfort (about 1 of 6 patients), nausea, vomiting, indigestion, heartburn, constipation and dyspepsia. The most common nervous system reactions are headache (1 of 15 patients), followed by dizziness and lightheadedness, tension and nervousness and drowsiness. Tinnitus occurs in 1 of 40 patients. Mild edema is observed in about 1 of 50 patients. Rash, including maculopapular eruptions or urticaria, develops in 1 of 30 patients; pruritus in about 1 of 50 patients. Small and transient decreases in hemoglobin and hematocrit, not associated with gastrointestinal bleeding, occur infrequently as well as a few cases of granulocytopenia. Also, see page 1115.

Safe use in children under 2 yr has not been established; the drug has been used safely and effectively in children over 2 yr. Use of the drug in pregnancy is not recommended and since it is secreted in human milk, its use by nursing mothers also is not recommended.

Dose (tolmetin equivalent)—*Adult, initially* 400 mg 3 times a day, subsequently adjusted to patient's response. Symptom control is usually achieved with a daily dosage of 600 to 1800 mg, given in 3 or 4 divided doses. Daily dosage exceeding 2000 mg for adults with rheumatoid arthritis or 1600 mg for adults with osteoarthritis has not been studied and therefore are not recommended. For the symptomatic treatment of juvenile rheumatoid arthritis, the initial dose for children 2 yr and older is 20 mg/kg/day in 3 or 4 divided doses. Therapeutic response can be expected in a few days to a week, with progressive improvement in succeeding weeks of therapy. If gastrointestinal symptoms occur, the drug should be given with meals, milk or antacids other than sodium bicarbonate.

Dosage Form—Tablets: 200 mg; Capsules: 400 mg (tolmetin equivalent; in each case). *Note:* each tablet contains 18 mg and each capsule contains 36 mg of sodium.

Other Nonsteroidal Anti-Inflammatory Drugs

Dimethyl Sulfoxide [Methyl sulfoxide [67-68-5] CH_3SOCH_3 (78.13); DMSO]—Prepared by air-oxidation of dimethyl sulfide in the presence of nitrogen oxides. A practically colorless and odorless, very hygroscopic liquid, boils at 189°; density of 1.100. Soluble in water, alcohol, ether or chloroform. *Uses:* An aprotic solvent with remarkable properties to enhance penetrance of many locally applied drugs. During the course of its agricultural use as a solvent it was discovered to relieve arthritic pain, and it soon became used rather widely and promiscuously in the topical treatment of various collagen diseases. The discovery of DMSO-induced lens opacities in animals resulted in termination of these uses. At present it is approved only for the treatment of *interstitial cystitis.* Locally applied DMSO, in concentrations above 50%, breaks down collagen, and has anti-inflammatory and local anesthetic effects, all of which probably contribute to relief of pain and improvement in bladder function and mucosal cytology. DMSO is converted to dimethyl sulfide, which imparts to the skin and breath a foul odor described as "garlic-like," but more offensive. No other side effects of intravesical instillation of 50% solutions have been reported but transient disturbances of color vision, photophobia, headache, nausea, diarrhea, urethral burning sensation on urination and allergies have occurred from topical application to the skin. *Dose: Intravesical,* as a 50% solution.

Gold Compounds

Most authorities prefer the gold compounds over the adrenal steroids or nonsteroidal anti-inflammatory drugs for the adjunctive treatment of selected cases of active rheumatoid arthritis. Gold compounds suppress or prevent, but do not cure, arthritis and synovitis. Although their exact mechanism is not known, localized high concentrations of gold are found in Kupffer cells and synoviocyte liposomes; this suggests that gold therapy may inhibit liposomal enzyme activity in macrophages and decrease macrophage phagocytic activity. Accumulation occurs with repeated administration and levels persist for many years in subsynovial tissues and in macrophages of many tissues. Macrophages are thought to be involved in the antigen process and in the interaction of helper T lymphocytes with antibody forming B lymphocytes. Whether or not this action is responsible for the effectiveness of gold compounds in arthritis is unknown.

The *oral* gold compound available (auranofin) contains 29% gold by weight, whereas the *parenteral* preparations (aurothioglucose; gold sodium thiomolate) contain 50% gold by weight. Before gold therapy is initiated, the patient's hemoglobin, erythrocyte, leukocyte, differential and platelet counts should be determined and a urinalysis done to serve as a basic reference. Urine should be analyzed for protein and sediment changes, and a complete blood count should be done prior to every administration or injection throughout the course of treatment.

Adverse reactions to gold therapy may occur at any time during treatment or many months after therapy has been discontinued. Common adverse reactions include *cutaneous:* dermatitis, pruritic eruptions, erythema, vesicular and exfoliative dermatitis, alopecia, loss of nails; *mucous membranes:* stomatitis, buccal ulcers, glossitis or gingivitis; *pulmonary:* interstitial pneumonitis, fibrosis, fever, rash, cough, shortness of breath, etc; *renal:* nephrotic syndrome, glomerulitis with hematuria and, rarely, renal failure; *hematologic:* granulocytopenia, thrombocytopenia, leukopenia, eosinophilia, hemorrhagic diathesis, hypoplastic and aplastic anemia; and *miscellaneous:* flushing, dizziness, sweating, nausea, vomiting and malaise. It is important to note